Aspirin in Primary Prevention: Who Should Get it?

Controversies and Advances in the Treatment of Cardiovascular Disease, The 18th in the Series

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“The aim of science is not only to

open the door to endless wisdom

but also to put a limit to endless error”

Galileo

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FDA-Approved Vascular Indications for Aspirin
October 23, 1998 Final Rule (63 FR 56803)

- Acute MI
  - *Reduce the risk of vascular mortality*
- Previous MI or USAP
  - *Reduce the combined risk of death and nonfatal MI*
- Ischemic Stroke or TIA
  - *Reduce the combined risk of death and nonfatal stroke*
- Chronic Stable Angina
  - *Reduce the combined risk of MI and sudden death*
- Coronary revascularization (CABG, PCI) and carotid endarterectomy
  - *Reduce cardiovascular risk*

Approved indications are only for secondary prevention!

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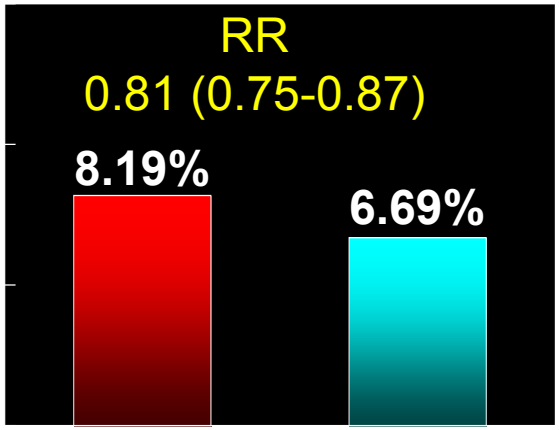
https://www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201-Professional%20Labeling.pdf

Aspirin in Secondary Prevention

Pooled Analysis from 16 RCTs (N=18,249)

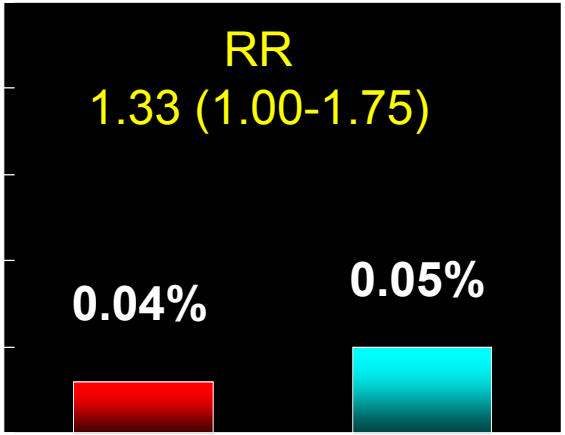
Serious Vascular Event (per year)



15 events/1000 pts

NNT=67

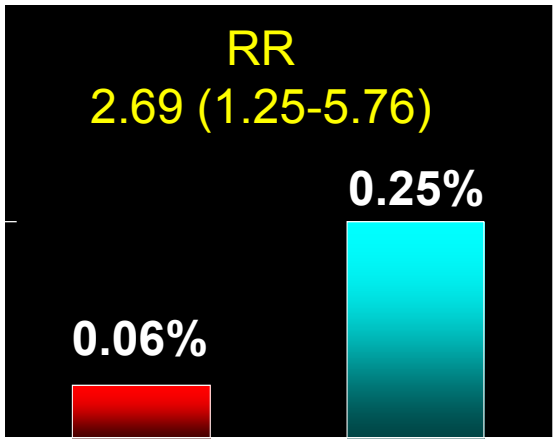
Hemorrhagic Stroke (per year)



0.1 events/1000 pts

NNH=10000

GI & EC Bleeding (per year)



2 events/1000 pts

NNH=526

Antithrombotic Trialists' (ATT) Collaboration, Lancet 2009;373:1849-60

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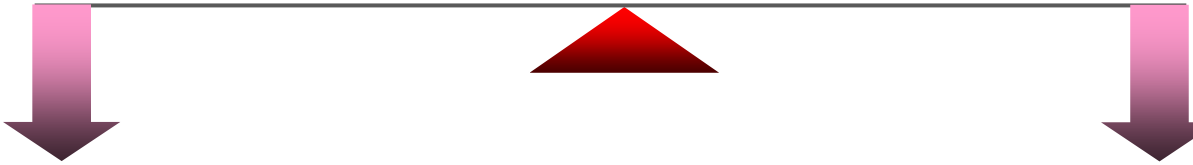
Aspirin Benefit-Risk Balance in CHD Prevention

10,000 Patients Treated with Aspirin per Year



Benefit

- Secondary prevention
  - 150 serious vascular events
  - 34 CHD death or 29 vascular death

Risk

- Secondary prevention
  - 19 major extracranial bleeds
  - 1 hemorrhagic stroke

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Aspirin in Primary Prevention: Regulatory History

	Study	Patient Population	Primary Efficacy Endpoint	Follow-up (mean, y)	Risk Ratio (95% CI)	P value
FDA 1998 Final Rule	**BDT 1988**	Healthy male doctors	CVD, MI, stroke	5.6	NA	NS
	PHS 1989	Healthy male doctors	CVD	5	0.96 (0.60-1.54)	0.87
FDA 2003 AdCom	**TPT 1998**	Men at high risk for CVD	CHD, MI	6.7	0.80 (0.65-0.99)	0.04*
	HOT 1998	Men & women with HTN	CVD, MI, stroke	3.8	0·91 (0·79-1·04)	0.17
	PPP 2001	Men & women >1 RF for CAD	CVD, MI, stroke	3.7	0·71 (0·48-1·04)	NS
	WHS 2005	Healthy females	CVD, MI, stroke	10	0.91 (0.80-1.03)	0.13
FDA 2014 BHC CP	**JPAD 2008**	Mean & women with DM, no CAD	CVD, MI, CVA, UA, PVD, new angina	4.4	0.80 (0.58-1.10)	0.16
	POPADAD 2009	Mean & women with DM, PAD	CVD, MI, stroke, amputation, critical limb ischemia	6.7	0.98 (0.76-1.26)	0.86
	AAA 2010	Mean & women with low ABI	CVD, MI, stroke, Revasc	8.2	1.03 (0.84-1.27)	NS

*alpha of 0.01

*after including silent MI, the reduction was no longer significant (P = 0.07)

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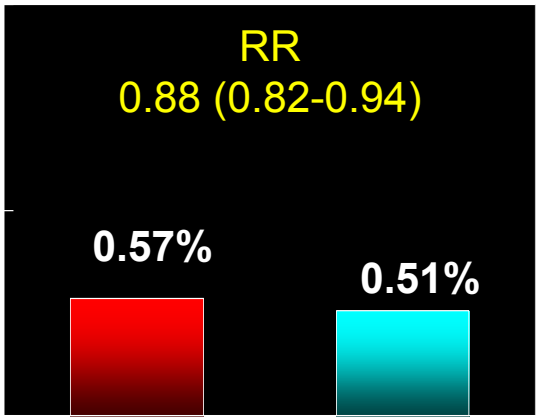
Aspirin in Primary Prevention

Pooled Analysis from 6 RCTs (N=95,000)

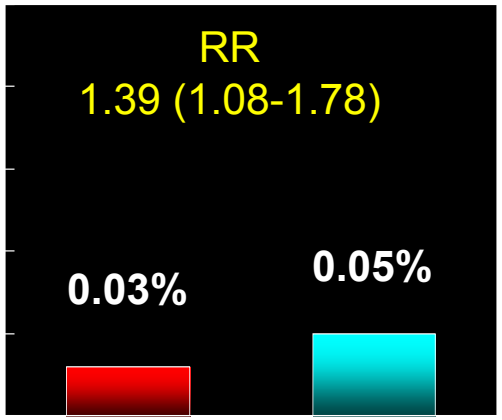
Serious Vascular Event (per year)



0.6 events/1000 pts

NNT=1667

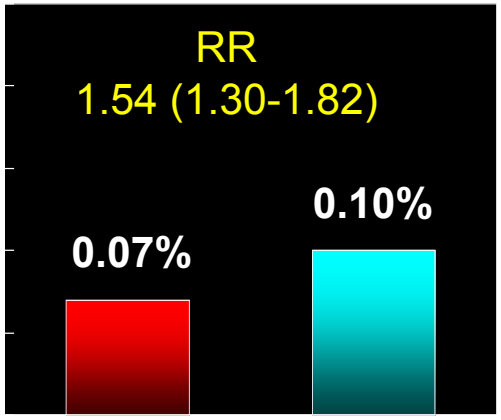
Hemorrhagic Stroke (per year)



0.2 events/1000 pts

NNH=5000

GI & EC Bleeding (per year)



0.3 events/1000 pts

NNH=3333

Antithrombotic Trialists' (ATT) Collaboration, Lancet 2009;373:1849-60

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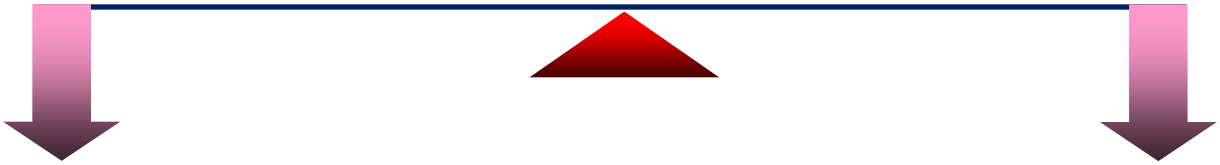
Aspirin Benefit-Risk Balance in CHD Prevention (2009)

10,000 Patients Treated with Aspirin per Year



Benefit

- **Primary prevention**
  - 6 serious vascular events
  - No impact on CHD or vascular death
- **Secondary prevention**
  - 150 serious vascular events
  - 34 CHD death or 29 vascular death

Risk

- **Primary prevention**
  - 3 major extracranial bleeds
  - 2 hemorrhagic strokes
- **Secondary prevention**
  - 19 major extracranial bleeds
  - 1 hemorrhagic stroke

Evidence for secondary prevention >>> primary prevention

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Aspirin in Primary Prevention of CVD

Which Guidelines to Trust?

Guideline	Risk category	Age/gender	Dose	Quality of evidence
USPSTF (2009)	10 yr MI >4% (♂) 10 yr stroke >3% (♀)	Men: 45-79y Women: 55-79y	80-100mg qd 80-100mg qod	A (high) A (high)
ASA/AHA (2010)	10 yr CVD: 6-10%	Men Women	81-100mg qd 81-100mg qod	Class I LOE A Class IIa LOE B (stroke in women)
ACCP (2012)	Mod-high CV risk	Men/women >50y	75-100mg qd	2B
CCS (2012)	Men/women without vascular disease	NA	NA 75-162mg qd	Class III LOE A Class IIb LOE C (↑ vascular/↓ bleed risk)
ESC (2016)	Men/women (- CVD)	NA	NA	Class III, LOE B
USPSTF (2016)	10 yr CVD >10%, 10 yr life expectancy, ↓ bleed risk	Men/women 50-59y Men/women 60-69y Men/Women: <50, >70y	80-100mg qd 80-100mg qd 80-100mg qd	B (moderate) C (low) I (insufficient)

- FDA has not approved ASA for primary prevention of CVD
  - December 2003 Ad Com vote: 11-3 against approval
  - 2003 BHC Citizen Petition denied by the FDA in May 2014

Aspirin in Primary Prevention of CVD
Overinterpretation of Weak Evidence

- Meta-analysis of small, inconclusive trials (false positive)
  - Primary endpoint NOT met in ANY trial
  - High likelihood of false-positive results from pooled analyses (PPV <50%)
  - FDA does not utilize meta-analyses for regulatory decision making
- Subgroup analysis (? credibility)
  - Only 3/11 ASA trials prespecified sex as a subgroup (? biological plausibility, no prior evidence)
  - Only 5/11 ASA trials adjusted for confounders
  - Formal test for interaction not performed in ASA trials
  - No adjustment for multiplicity in ASA trials
- Post hoc analysis (false positive)
  - WHS yielded a null result with respect to PEP (CV death, nonfatal stroke or MI)
  - Significant benefit for nonfatal stroke but not CV death or nonfatal MI
  - Alpha error already spent for null PEP, so nonfatal stroke finding likely a false +ive result

Aspirin in Primary Prevention: Post-2014 FDA CP

Primary Efficacy Endpoint

Study	Patient Population	Primary Efficacy Endpoint	Follow-up (mean, y)	Risk Ratio (95% CI)	P value
JPPP 2014 (N=14,464)	60-85y, h/o HTN, DM, HLD (51% on statins)	CVD, MI, stroke	5.02 **(stopped for futility)**	0.94 (0.77-1.15)	0.54
ASCEND 2018 (N=15,480)	Age ≥40y and DM (75% on statins)	Serious vascular event (Vascular death, MI, Stroke)	7.4	0.88 (0.79-0.97)	0.01
ARRIVE 2018 (N=12,546)	Men >50, women >60 at moderate risk for CVD (10yr-PCE ASCVD risk 17.3%) (43% on statins)	CVD, MI, UA, Stroke/TIA	5	0.96 (0.81-1.13)	0.61
ASPREE 2018 (N=19,114)	Men & women >70y without CV disease, dementia or physical disability (34% on statins)	Death, dementia or permanent physical disability	4.7 **(stopped for futility)**	1.01 (0·92-1·11)	0.79

- Primary endpoint met in only 1 trial (ASCEND)
- Two trials stopped for futility (JPPP, ASPREE)

Aspirin in Primary Prevention: Post-2014 FDA CP

Benefit-Risk Assessment

Study	Endpoint	Aspirin	Placebo	ARD	Risk Ratio (95% CI)	P value
JPPP 2014 (N=14,464)	CV death, MI, Stroke	2.77%	2.96%	-0.19%	0.94 (0.77-1.15)	0.54
	Extracranial bleeding	0.86%	0.51%	+0.35%	1.85 (1.22-2.81)	0.004
ASCEND 2018 (N=15,480)	Vascular death, MI, Stroke	8.5%	9.6%	-1.1%	0.88 (0.79-0.97)	0.01
	Major bleeding	4.1%	3.2%	+0.9%	1.29 (1.09-1.52)	0.003
ARRIVE 2018 (N=12,546)	CVD, MI, UA, Stroke/TIA	4.3%	4.5%	-0.2%	0.96 (0.81-1.13)	0.61
	GI bleed	0.97%	0.46%	+0.41%	2.11 (1.36-3.28)	0.0007
ASPREE 2018 (N=19,114)	Death, dementia or permanent physical disability	21.5/ 1000PY	21.2/ 1000PY	+0.3/ 1000PY	1.01 (0·92-1·11)	0.79
	Major hemorrhage	3.8%	2.9%	+1.0%	1.38 (1.18-1.62)	<0.001

Benefit-risk balance of aspirin not desirable in any trial

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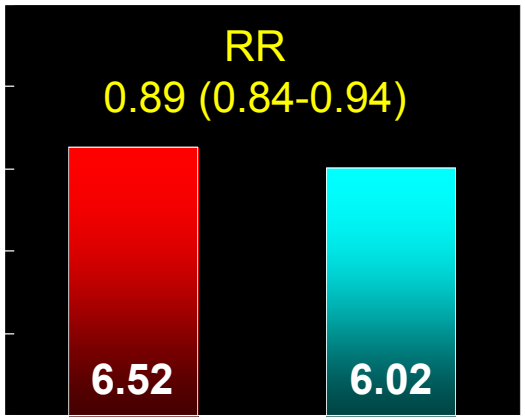
Aspirin in Primary Prevention

Pooled Analysis from 13 RCTs (N=164,225)

MACE (per 1000PY)

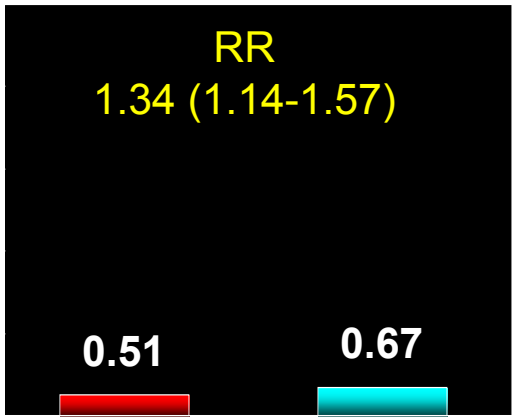


0.5 events/1000 PY

NNT_{5y}=241

↑ CV risk NNT_{5y}=160

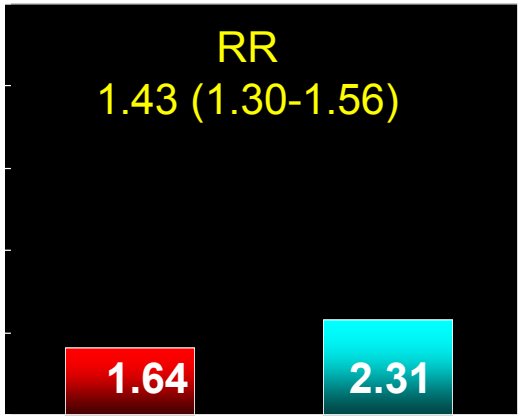
Intracranial Bleeding (per 1000PY)



0.16 events/1000 PY

NNH_{5y}=927

Major Bleeding (per 1000PY)



0.67 events/1000 PY

NNH_{5y}=210

NNH_{5y}=152

Zheng SL et al. *JAMA.* 2019;321(3):277-287

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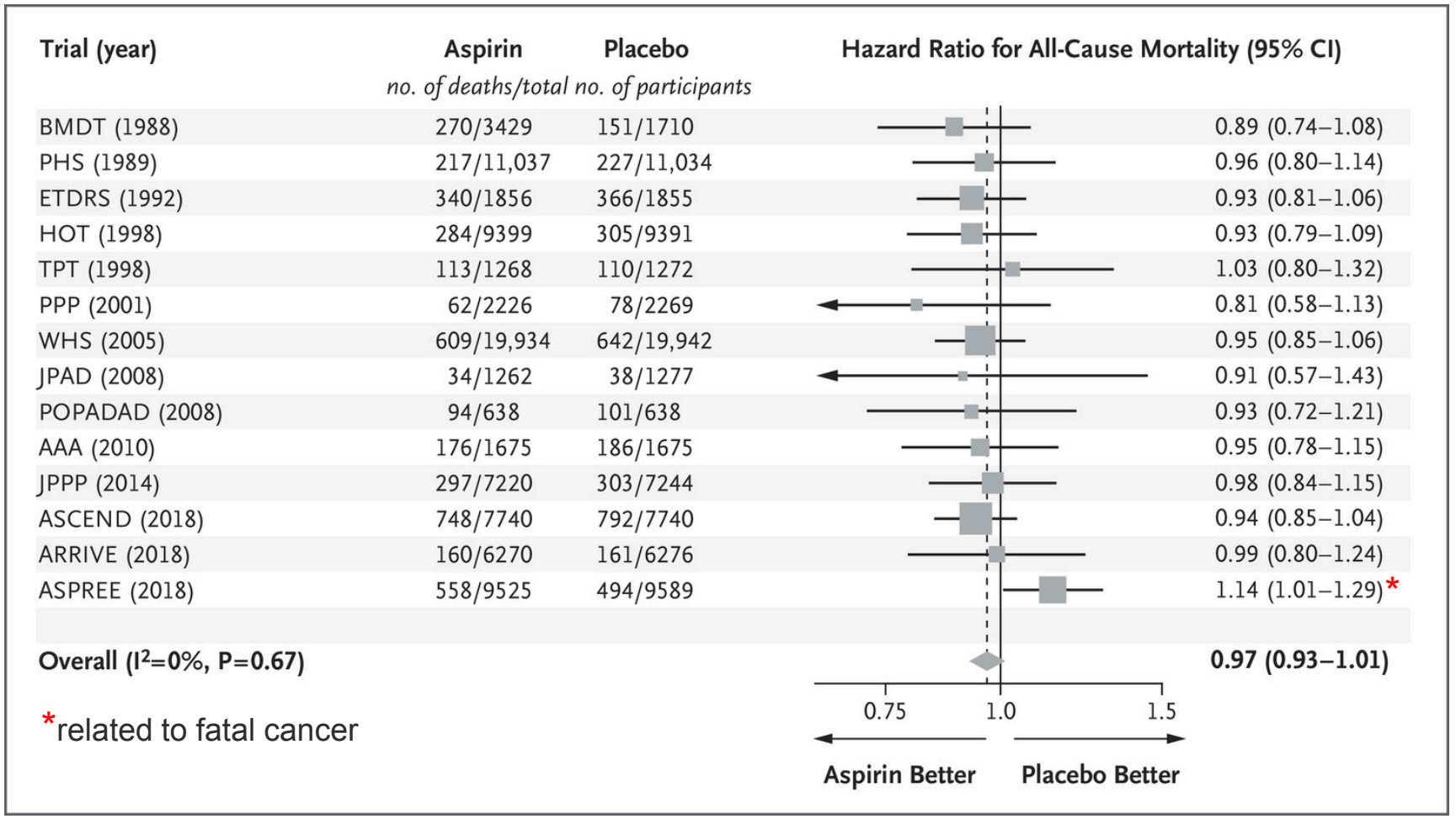
Aspirin and All-Cause Mortality in 14 Primary Prevention Trials



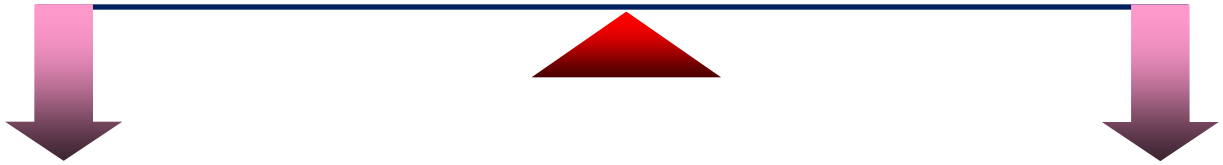
*related to fatal cancer

Null effect on mortality with aspirin in primary prevention

PM Ridker. N Engl J Med 2018;379:1572-1574.

Aspirin Benefit-Risk Balance in CHD Prevention (2019)

10,000 Patients Treated with Aspirin per Year



Benefit

- **Primary prevention**
  - 5 MACE, 3MI, 3 Ischemic strokes
  - No impact on all-cause or CV mortality or cancer
- **Secondary prevention**
  - 150 serious vascular events
  - 34 CHD death or 29 vascular death

Risk

- **Primary prevention**
  - 7 major extracranial bleeds
    - 5 major GI bleeds
  - 2 intracranial bleeds
- **Secondary prevention**
  - 19 major extracranial bleeds
  - 1 hemorrhagic stroke

Evidence for secondary prevention >>> primary prevention

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Aspirin in Primary Prevention in 2019

Latest Guidelines

Guideline	Risk category	Age/gender	Dose	Quality of evidence
ADA (2019)	DM + high ASCVD risk, but not ↑ bleeding risk	Men/Women: 50-70y	75-162mg qd	C (low)
ACC/AHA (2019)	Higher ASCVD risk, but not ↑ bleeding risk	Men/Women: 40-70y	75-100mg qd	Class IIb LOE A
	Low/moderate risk	Men/Women: >70y	75-100mg qd	Class III LOE B-R
	↑ bleeding risk	Men/women: any age	75-100mg qd	Class III LOE C-LD
ESC/EASD (2019)	DM men/women at very high CV risk* and absence of clear contraindications	NA	75-100mg qd	Class IIb, LOE A
	DM men/women at moderate CV risk**	NA	75-100mg qd	Class III, LOE B

*other target organ damage or ≥3 major risk factors or early onset T1DM of >20y duration
**young patient (T1DM <35y or T2DM <50y) with <10y DM duration, no other risk factors

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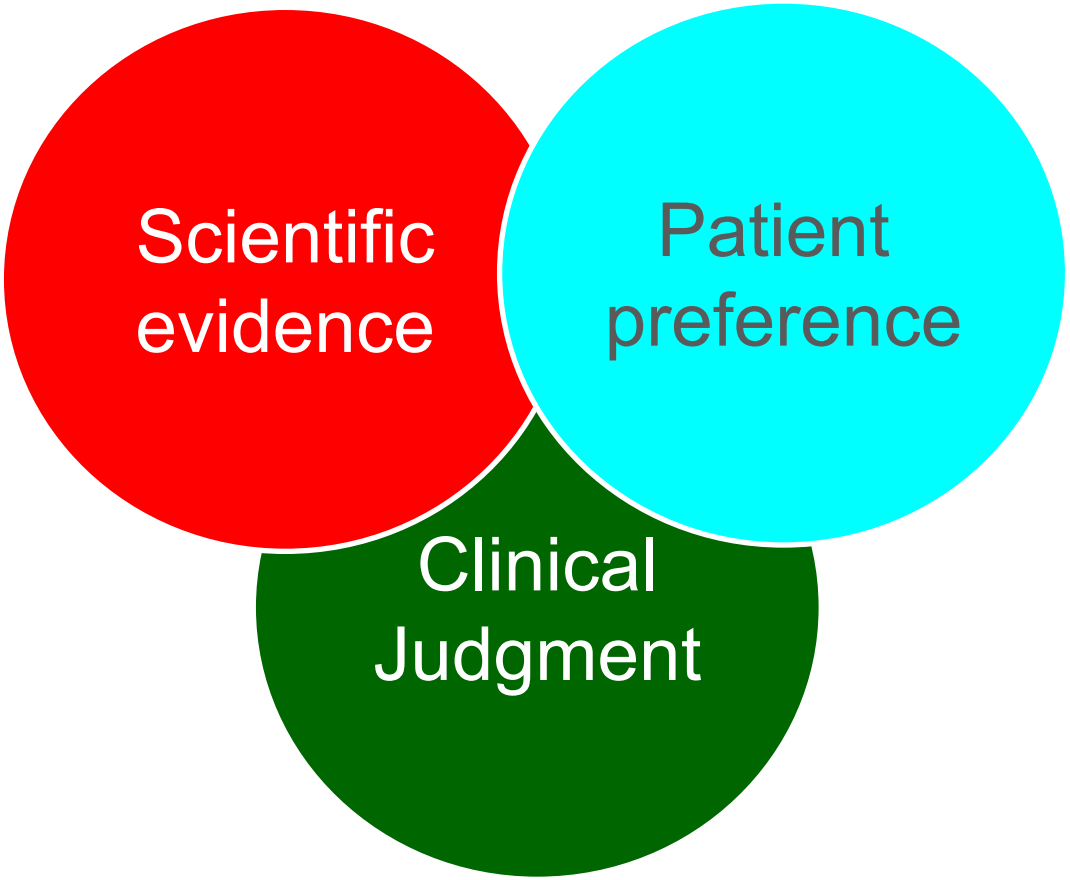
Aspirin in Primary Prevention of CVD

Evidence-Based" Not "Evidence-Bound"

Three Key Dimensions



"Use of aspirin for primary prevention should be based on benefit-risk tradeoff and individual patient preference and value judgment"